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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,607	09/26/2003	Jonathan A. Ellman	045413-0113	9898

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/670,607	ELLMAN ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *3,6,7,14,15 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,8-13,16-20 and 23* is/are rejected.

7)☒ Claim(s) *21 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/26/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on September 19, 2004.

Status of the Claims

2. Claims 1-24 were pending in the present application.

3. Applicant's *specifically* elected species (Subgroup 4 = ELISA, see attached Interview Summary; Subgroup 5 = Applicants elect a disulfide linking group) were found in the art. Furthermore, Applicant's *specifically* elected species (Subgroup 1 = CD4, Subgroup 2 = 252 member library of disulfide compound having core structure CTBF-S-S-R^8 wherein R^8 is straight chain alkyl of 1 to 10 carbon atoms substituted with amino and the CTBF-S-S-R^8 has less that 500 Daltons, Subgroup 3 = 6-boromo chromone without the aldehyde linking group) were searched and were not found in the prior art. Thus, the search was expanded to non-elected species, which *were* found in the prior art, see rejections below. Also, see MPEP § 803.02 (emphasis added):

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species.*** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-

type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

4. Claims 3, 6-7, 14-15 and 24 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, the requirement having been traversed in the 9/24/04 response (see below i.e., ***Response to Restriction and/or Election of Species***; see also attached Interview Summary).

5. Therefore, claims 1-2, 4, 5, 8-13, 16-23 are examined on the merits in this action.

Response to Restriction and/or Election of Species

6. Applicant's election of species in the 9/24/04 Response ***with traverse*** is acknowledged.

7. The election of species traversal is on the ground(s) that "there is no undue burden to search of all the subject matter of the claims" (e.g., see 10/19/04 Response, page 2, lines 1-2).

8. These arguments were fully considered but were not found persuasive. The Examiner's position is that the species are distinct, each from the other, because the structures and modes of action of each of the species encompassed are different. They would also differ in their reactivity and/or mechanism and/or the products made. For example, the species of target biological molecule (TBM) have different structures and functions and, as a result, are separately

classified (e.g., TBM = enzyme in class 435, subclass 183+; TBM = hormone in class 530, subclass 397; TBM = antibody in class 530, subclass 387.1+, etc.). Likewise, the library of small organic molecules can also be separately classified into hundreds of different class and subclasses depending on the structure of the library members and/or their function (e.g., Library = for peptide in class 435, DIG 35; peptide-nucleic acid in class 435, DIG 36, etc.). The species of candidate target biological fragments, Subgroup 3, and linking group, subgroup 5, could be classified into hundred of different classes and subclasses depending their structure (e.g., classes 532-570 drawn to various organic molecules). Finally, the species of detection can also be separately classified (e.g., Subgroup 4 = NMR is in class 436, subclass 173, Subgroup 4 = X-ray crystallography is in class 378, subclass 73, etc.). Thus, the different species would require different searches and there is no expectation that the searches would be coextensive. Therefore this does create an undue search burden.

9. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

10. The information disclosure statement filed September 26, 2003, fails, in part, to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because two publications cited therein, numbered A19, A22 and A26, lack publication dates and/or page numbers, a necessary element for consideration. While the other patent and other publications cited therein, and supplied, therewith, have been considered as to the merits, these three publications have not. Applicant is advised that the date of any re-submission of these citations contained in this

information disclosure statement or the submission of the missing element – their publication dates – will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPE § 609 C(1).

The other references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Objections to the Claims

11. Claim(s) 21 and 22 are objected to objected to as being dependent upon a rejected base claims, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-2, 4, 8-13, 16-18 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Kirkpatrick (U.S. Patent 6,552,060) (Filing Date is **August 11, 1998**) (Provisional

Filing for 60/055,201 **August 11, 1997**) (see http://portal.uspto.gov/externalportal/pair for public access to priority documents).

For ***claim 1***, Kirkpatrick (see entire document) discloses screening asymmetric disulfides for the inhibition of TR/trx and their subsequent use as potential therapeutic agents to inhibit abnormal cellular proliferation, which anticipates the claimed invention. For example, Kirkpatrick discloses **(a)** contacting the TBM with individual members of a library of the CTBF (e.g., see column 23-24, especially Table 4 wherein TR/trx is disclosed as the TBM and A1-J28 are disclosed as the CTBFs; see also Figure 5; see also columns 7-11). In addition, Kirkpatrick discloses **(b)** detecting and determining which CTBF's bind to the TBM (e.g., see column 23, Table 4 wherein binding data is presented). Kirkpatrick further disclose **(c)** selecting CTBF's that bind to the TBM (e.g., see columns 23-24 wherein the disulfides were further selected for cytotoxicity studies; see more generally Summary of Invention wherein "selected" compounds are used as therapeutic agents; see also claims 12-19 wherein several compounds with favorable therapeutic agents are "selected" as preferred embodiments). Finally, Kirkpatrick discloses a library represented by formula CTBF-S-S-R^8 wherein R^8 is, for example, a straight chain alkyl or branched aminoalkyl or hydroxyalkyl (e.g., see figure 5; see also figures 9-11, especially figure 10 wherein R'=A, B, C, D, M and O; see also paragraph bridging columns 4-5; Table 3, especially compounds F-27, M-13 and M-29; see also column 22; see especially claims 8 and 19 wherein R^8 represents branched alkyls substituted with amino or hydroxy groups; see also column 4, last paragraph wherein n-

butyl imidazolyl disulfide is disclosed; see also column 5, line 5 wherein a straight chain hydroxyalkyl is disclosed).

For ***claim 2***, Kirkpatrick discloses "quantifying" the binding association (e.g., see column 23, Table 4).

For ***claim 4***, Kirkpatrick discloses an "in vitro" biological assay (e.g., see column 23, paragraph 1 wherein assay was performed "in vitro" on a 96 well plate).

For ***claims 8, 20***, Kirkpatrick discloses a library wherein each CTBF further contains a second LG (e.g., see column 24, especially Table 6 wherein (bis) disulfides are disclosed of formula R_1-S-S-Y-S-S-R_2 that contain two -S-S- LG groups).

For ***claim 9***, Kirkpatrick discloses linking at least two of the selected CTBF's or analogs thereof (e.g., see Table 6, entry 3/KK wherein two thiadiazole CTBFs are joined).

For ***claim 10***, Kirkpatrick discloses the use of analogs (e.g., see column 18, lines 9-20, "Based on the information provided by studying the asymmetrical imidazoyl disulfides (i.e., VI-2) a parallel combinatorial synthetic method was used to produce a large number of disulfide analogues to study specificity and applicability to the thioredoxin ...").

For ***claim 11***, Kirkpatrick discloses linking the selected CTBF's to a second compound (e.g., see column 24, especially Table 6 wherein (bis) disulfides are disclosed of formula R_1-S-S-Y-S-S-R_2 which contain R_1, Y and R_2 compounds).

For ***claims 12-13***, Kirkpatrick discloses thioredoxin reductase (TR), which is a NADPH-dependent selenium containing flavoprotein that catalyzes the reduction of thioredoxin (Trx) (e.g., see figure 5).

For ***claims 16-17***, Kirkpatrick discloses, for example, the compound in claims 12-19, which have molecular weights of less than 500 Daltons (see also Table 4; see also Figures 5 and 9-11).

For ***claim 18***, Kirkpatrick discloses a disulfide library with greater than 100 members (e.g., see entries in Tables 4-6; see also Figures 5 and 9-11).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-2, 4, 5, 8-13, 16-20 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirkpatrick et al. (U.S. Patent 6,552,060) (Filing Date is **August 11, 1998**) and Fischli et al. (US Patent No. 4,766,133) (Date of Patent is **August 23, 1988**) and Das et al. (Das, K. C.; White, C. W. "Detection of thioredoxin in human serum and biological samples using a sensitive sandwich ELISA with digoxigenin-labeled antibody" Journal of Immunological Methods February 1, 1998, 211, 9-20).

For ***claims 1-2, 4, 8-13, 16-18 and 20,*** Kirkpatrick teaches all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 1-2, 4, 8-13, 16-18 and 20.

The prior art teachings of Kirkpatrick differ from the claimed invention as follows:

For ***claim 5***, the prior art teachings of Kirkpatrick et al. differ from the claimed invention by not specifically reciting the use of ELISA.

For ***claims 19 and 23***, the prior art teachings of Kirkpatrick et al. differ from the claimed invention by not specifically reciting R^8 = straight chain alkyl with 1-10 carbon atoms substituted with an amine.

However, Fischli et al. teach the following limitations that are deficient in the combined teachings of Kirkpatrick et al. and Konings et al.:

For ***claim 5***, Das et al. teach the use of ELISA to detect thioredoxin.

For ***claims 19 and 23***, Fischli et al. (see entire document) teach disulfide compounds with R^8 = straight chain alkyl with 1-10 carbon atoms substituted with an amine (e.g., see Fischli et al., column 13, compound G).

It would have been obvious to one skilled in the art at the time the invention was made to use the combinatorial screening techniques against thioredoxin reductase/thioredoxin targets as taught by Kirkpatrick (e.g., see Kirkpatrick et al., column 22, paragraph 1; see also column 23, paragraph 1) with the disulfides as taught by Fischli et al. (e.g., see Fischli et al., column 12, compound G) because Kirkpatrick teaches that disulfides with benzimidazole and/or imidazole rings are a preferred embodiment for high throughput screening against thioredoxin reductase/thioredoxin targets (e.g., Kirkpatrick et al., abstract, see especially column 18, lines 24-25), which would encompass the compounds disclosed by Fischli et al. Furthermore, one of ordinary skill in the art would have been motivated to use the compounds disclosed by Fischli et al. because Fischli et al. teach that their disulfides are "gastric acid secretion-inhibiting and/or mucosa-protecting" (e.g., see column 1, lines 66-67), which would be beneficial because Kirkpatrick teach the therapeutic application of disulfides to the stomach and/or gastrointestinal tract which would require such protection (e.g., see Kirkpatrick et al., "The term 'cancer' refers to ... stomach cancer"; see also column 3, line 39; see also column 8, line 58). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because both references teach the application of structurally similar compounds (e.g., both references teach asymmetric disulfides with heteroaromatic rings).

In addition, it would have been obvious to one skilled in the art at the time the invention was made to use the combinatorial screening techniques against thioredoxin reductase/thioredoxin targets as taught by Kirkpatrick (e.g., see Kirkpatrick et al., column

22, paragraph 1; see also column 23, paragraph 1) with the thioredoxin ELISA assay disclosed by Das et al. because Kirkpatrick requires the detection of thioredoxin in their assay (e.g., see Kirkpatrick et al., column 23, paragraph 1). Furthermore, one of ordinary skill in the art would have been motivated to use the ELISA assay because according to Das et al. said assay "is easy to use, rapid, reproducible, but above all quantitative, specific and sensitive" (e.g., see Das et al., page 19, column 1, first full paragraph). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Das et al. provide a method for successfully detecting the same compound that is disclosed in Kirkpatrick (i.e., thioredoxin).

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
January 8, 2005

PADMASHRI PONNALURI
PRIMARY EXAMINER